UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,301	02/17/2000	Joseph C. Glorioso	204001	7569

7590 02/11/2003

M Daniel Hefner
Leydig Voit & Mayer LTD
Two Presidential Plaza Suite 4900
180 North Stetson
Chicago, IL 60601-6780

EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,301	GLORIOSO ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 11/14/02 as Paper No. 12, in which claims 1-16 and 21-30 were cancelled and new claims added (claims 31-74). Claims 31-74 are pending in the instant application.

Any rejection of record in the previous office action, mailed 6/5/02 as Paper No. 11, not addressed in the instant action is withdrawn. Upon further review of the prior art, it has been determined that additional rejections are appropriate base upon the teachings of the prior art. Because these new rejections were not necessitated by applicants' amendment of the claims in Paper No. 12, this action is not final.

Priority

It is noted that the instant application claims priority to the provisional U.S. Application No. 60/120,391, filed 02/17/1999. However, upon further review of the provisional application, it is apparent there is no support in 60/120,391 for embodiments of the currently claimed invention featuring conditionally active rep proteins. Therefore, the instant claims comprising the limitation of a conditionally active rep protein are accorded priority to the filing date of the instant application (i.e. 2/17/2000). This priority date is after publication of the Gavin et al reference cited in the rejections that follow (Journal of Virology, Vol. 73, No. 11, pages 9433-9445 November 1999).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection.**

The rejected claims all comprise a limitation of a rep gene encoding a conditionally active rep protein. The conditionally active rep protein can be obtained from any one of the 4 rep proteins encoded by the AAV rep gene (i.e. rep 78, rep68, rep62 and rep40). In addition, the rep protein can be from any AAV source of any serotype. Thus, the rejected claims encompass a broad genus of rep proteins that must be active under one set of conditions and which also must be functionally inactive under a different set of conditions. The difference in conditions can be any variable such as ionic strength, temperature, metabolic factor, etc.

The instant specification provides literal support for the concept of conditionally active rep proteins for each of rep78, rep68, rep62 and rep40. There is no description, however, of any specific rep mutant that is conditionally active. The specification simply incorporates by reference the teachings of Gavin et al (Journal of Virology, Vol. 73, No. 11, pages 9433-9445 November 1999) as providing support for the concept of conditionally active rep mutants.

Gavin et al teach the mutagenesis and selection of rep78/68 mutants via alanine substitution that are temperature sensitive (i.e. D40,42,44A-78) and Mg2+ sensitive (i.e. D412A-78, D412A-68). Gavin et al teach that the rep68 and 78 proteins are nearly identical except for a C-terminal sequence generated by differential RNA splicing (page 9433, first paragraph). Gavin

et al teach that there is as yet no crystal structure available for AAV rep proteins (page 9440, column 2, first full paragraph). Gavin et al teach that their D40,42,44A-78 mutant is the first demonstration of a rep temperature-sensitive (ts) mutant for AAV rep. Although the D412A mutation is described as a "nonconditional" mutation (e.g. the Abstract), the mutant in rep78 demonstrated a reduced ability to support replication in vivo as well as reduced endonucleolytic activity in vitro for rep68 (e.g. Figures 5 & 6). Gavin et al teach that they have shown that increasing intracellular Mg2+ levels can increase the replication activity of D412A-78 in an Mg2+-dependent manner, indicating that this mutant can be more active depending upon cellular conditions (page 9443, first paragraph). Thus, Gavin et al provide description of two specific embodiments of Rep78/68 that are conditionally active.

Gavin et al do not, however, provide a basis for one of skill in the art to extrapolate from their results in order to predictably envision additional specific embodiments of the claimed invention. For example, it is noted that the single isolated mutant that gives rise to a temperature-sensitive phenotype comprises three separate alterations of the rep protein. In addition, Gavin et al introduced a mutation into another putative Mg2+-binding pocket of the rep protein (i.e. E465A) to test the relevance of this putative site on rep78/68 activity. The activity of this mutant was similar to that of wt rep78/68. Thus, it is not reliably predictable, based upon the teachings of Gavin et al, for one of skill in the art to envision which mutation, or combination of mutations, will affect the structural/functional characteristics of an AAV rep protein to give rise to a phenotype that is active under one set of conditions and not others.

Given that the specification does not provide any description of specific embodiments of conditionally-active rep proteins, except to cite the Gavin et al reference, and given that the prior

art provides only two specific embodiments of conditionally-active AAV rep proteins, one of skill in the art would not have had a structural/functional basis upon which to reliably predict the structural/functional characteristics of additional embodiments of the claimed invention (e.g. conditionally active mutants of rep40 or rep62). Thus, one of skill in the art would have not been able to envision a sufficient number of specific embodiments of the claimed rep proteins to describe the broadly claimed genus of such conditionally active proteins. Therefore, one of skill in the art would reasonably have concluded that applicants were not in possession of the broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 70-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 70 is unclear in that it recites "...further comprises an ITR cassette..." This limitation is indefinite in that claim 54, upon which claim 70 is ultimately dependent, already specifies that the composition has an ITR cassette, making it unclear whether there necessarily is another ITR cassette present in the composition. Upon reading the specification, it appears that the cited limitation from claim 70 is intended to specify an **additional** ITR cassette. It would be remedial to amend the claim to clearly indicate that an additional ITR cassette is present in the claimed composition.

Similarly, claim 71 recites the limitation that the ITR cassette of claim 70 is present within an HSV vector. It is unclear whether this HSV vector is the same recited in claim 54, or and additional HSV vector. It appears upon reading the specification that an additional, different HSV vector is intended by the recited limitation. It would be remedial to amend the claim language to clearly indicate whether there is an additional, different HSV vector intended by the cited limitation of claim 71.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The claimed invention is drawn towards a recombinant herpes simplex virus (HSV) comprising an adeno-associated virus (AAV) rep gene wherein the rep gene comprises a promoter controlling expression of a sequence encoding a rep polypeptide, and wherein either the promoter or the rep polypeptide is conditionally active. The rep protein can be rep78, rep68, rep62 or rep40. The promoter can be inducible or tissue-specific. The recombinant HSV can comprise AAV ITR sequences flanking a non-AAV sequence. The HSV vector can be deficient in at least one essential HSV gene.

In the specification, the term HSV is described as encompassing any herpes simplex virus strain, but excluding "amplicons", where the HSV comprises an HSV origin of replication, an HSV-derived packaging sequence and sufficient machinery to permit the virus to replicate within

permissive cells without the need for a helper HSV or plasmid sequences (e.g. page 4, lines 26-35). The specification teaches that the term "HSV" further encompasses strains having deletions in essential genes such that the HSV vector of the invention can only be replicated in permissive cells (e.g. pages 4-5, bridging paragraph). It is unclear from reading the specification as to at what point the number of mutations (e.g. deletions) of the HSV genome results in an "amplicon" as defined by the specification. For example, amplicons described in the references below could be replicated into HSV-1 virions by cells comprising complementing HSV-1 sequences integrated into the packaging cell genome. The issue is further clouded by the fact the implied definition of an amplicon as being a nucleic acid that does not comprise enough HSV machinery to permit the virus to replicate within permissive cells without the use of a helper virus or plasmid sequences appears to be contrary to the art. The art defines an "amplicon" as a term for any small, replicating DNA fragment (see the definition attached to Paper No. 11 from the OneLook On-Line Medical Dictionary at http//www.onelook.conv). Read broadly, the claims thus encompass an HSV virus comprising an amplicon that possesses an HSV origin of replication, an HSV packaging sequence and an AAV rep gene under the control of a "conditionally active" promoter.

Claims 31-36, 39, 42-43, 45-51, 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al (reference AQ on Paper No. 4) (WO 95/06743; see the entire application) in view of Kotin (Human Gene Therapy, Vol. 5, pages 793-801, 1994, see the entire reference) and Gavin et al (Journal of Virology, Vol. 73, No. 11, pages 9433-9445 November 1999; see the entire reference). **This is a new rejection.**

Dong et al teach the construction of helper viruses for production of rAAV that comprise genes essential for AAV replication. Dong et al teach that the helper viruses of their invention can be derived from adenovirus or one of several different types of viruses classified in general as "herpesvirus", including HSV (page 6, lines 16-28). Dong et al teach that these helper viruses can either be replication competent (i.e. comprising viral packaging sequences and an origin of replication) or replication defective (page 15, lines 19-29). Dong et al specifically teach that the herpesviral helper viruses of their invention will comprise one or more of the AAV rep, lip and cap genes (page 7, lines 8-20). Dong et al teach that these genes can be inserted into the helper virus genome at positions where either essential or nonessential genes from the helper virus genome have been deleted (page 7, lines 21-32). The AAV rep, lip or cap genes can be under the control of either "natural" AAV promoters or heterologous promoters (e.g. the HSV tk promoter). Dong et al teach that the choice of promoter is not critical so long as the promoter effectively directs expression of the AAV gene or genes, and that the promoter can be a constitutive promoter (e.g. page 8, lines 20-27; page 9, lines 4-14). Dong et al teach a prophetic example for insertion of AAV rep, lip and/or cap sequences into the genome of HSV featuring the HSV vector R7020. R7020 features deletion of approximately 700 bp from the domain of the thymidine kinase gene and all of the sequences from the 3' end of the IE63 (α27) gene to the α4 gene in the reiterated sequence of the S component of the HSV genome. The authors teach that the rep-lip-cap genes can be inserted into, at least, either of two positions including the site between the inserted tk gene and the HSV-2 DNA sequences and the site of the deletion of the natural tk gene (e.g. Example VI(1) page 44). The wildtype rep gene would be expected to produce each of the four rep proteins normally produced by AAV.

Dong et al do not explicitly teach the use of a conditionally active rep protein and/or an inducible promoter.

Kotin teaches that establishment of cell lines with high copy numbers of rep genes had not been accomplished as of 1994 and that the reason for this was the evident cytotoxicity of rep expression. Kotin further teaches that 293 cell lines stably transfected with an inducible rep gene under control of the metallothionine promoter have been described and reported to complement rep$^-$ AAV (page 798, 2nd paragraph).

The teachings of Gavin et al are described above and applied as before, except: Gavin et al teach that the availability of the conditionally active ts and non-ts proteins described in their work should provide novel approaches for generating rAAV packaging systems, including herpes simplex helper viruses and packaging systems (e.g. final paragraph, page 9443). Gavin et al further teach that at permissive temperatures, the D40,42,44A-78 mutant is more effective than the wt rep protein at replicating AAV (e.g. Table 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Dong et al to include the use of a conditionally active rep protein because it was known in the art at the time of filing that over-expression of rep protein in cells can be cytotoxic (e.g. the teachings of Konti), and because Gavin et al teaches that it is within the skill of the art to use a conditionally active rep protein to replicate rAAV at permissive temperatures at efficiencies that are comparable to, or better than, wt rep protein. One would have been motivated to do so in order to receive the expected benefit of minimizing the toxic effects of expressing rep protein in the packaging cells taught by Dong et al while maximizing expression of the desired rep protein. Absent any evidence to the contrary, there would have

been a reasonable expectation of success in utilizing the rep mutants taught by Gavin et al in the methods taught by Dong et al for producing rAAV.

It would have been obvious to one of ordinary skill in the art at the time of invention to include an inducible promoter to regulate transcription of the AAV rep gene in the constructs taught by Donti et al because Kotin teaches that expression of AAV rep can be cytotoxic to cells and that one can overcome this problem by incorporating an inducible promoter to regulate its expression. One would have been motivated to do so in order to receive the expected benefit of being able to inducibly regulate the expression of the rep gene from the constructs of Donti et al so as to avoid the potential cytotoxic effects of rep expression, as taught by Kotin. Absent any evidence to the contrary, and based upon the teachings above and state of the art at the time of filing, one would have had a reasonable expectation of success in using an inducible promoter (e.g. the metallothionine promoter) to regulate expression of the rep gene from the constructs taught by Donti et al for preparation of rAAV.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dong et al (reference AQ on Paper No. 4) (WO 95/06743; see the entire application) in view of Kotin (Human Gene Therapy, Vol. 5, pages 793-801, 1994, see the entire reference) and Gavin et al (Journal of Virology, Vol. 73, No. 11, pages 9433-9445 November 1999; see the entire reference), and further in view of Glorioso et al (U.S. Patent No. 5,998,174; see the entire patent).. **This is a new rejection.**

The teachings of Dong et al, Konti and Gavin et al are described above and applied as before, except: the references do not teach and embodiment featuring the alteration or deletion of

the ICP27 gene for constructing an HSV-1/AAV hybrid helper virus comprising a gene encoding a conditionally active rep protein.

Glorioso et al teach the construction and use of a variety of HSV vectors (e.g. Abstract). Glorioso et al teach that the HSV genome is well characterized and that one can make deletion mutations in essential genes (in particular ICP4 & ICP27) such that the HSV vector is replication-defective unless grown in a host cell providing the missing translation product or products (column 2, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the recombinant HSV vector constructed according to the teachings of the combined references above to include a deletion of at least part of the ICP27 gene because Dong et al teach that it is within the skill of the art to make the helper-virus constructs of their invention comprising deletions of any non-essential or essential gene (e.g. glycoprotein H or ICP27) so long as the essential gene products are provided in trans during replication of the helper virus and because Glorioso et al specifically teach that it is possible and desirable to make recombinant HSV vectors comprising a deletion of at least a portion of the ICP27 gene. One would have been motivated to do so in order to receive the expected benefit of limiting the induction of herpes viral replication during the methods taught by the combination of the Dong et al and Glavin et al references for production of rAAV with the HSV-helper virus. Absent any evidence to the contrary, there would have been a reasonable expectation of success in incorporating a deletion in the ICP27 gene, as taught by Glorioso et al, in the recombinant HSV vectors constructed according to the teachings of the above cited references for expression of AAV rep and cap during production of high-titer rAAV stocks.

Conclusion

No claims are allowed. This action is not final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
February 10, 2003